4 **Sany J**, Anaya JM, Canovas F, Combe B, Jorgensen C, Saker S, *et al*. Influence of methotrexate on the frequency of postoperative infectious complications in patients with rheumatoid arthritis. *J Rheumatol* 1993;**20**:1129–32.
5 **Marchal L**, D'Haens G, Van Assche G, Vermeire S, Noman M, Ferrante M, *et al*. The risk of post-operative complications associated with infliximab therapy for Crohn's disease: a controlled cohort study. *Aliment Pharmacol Ther* 2004;**19**:749–54.
6 **Bibbo C**, Goldberg JW. Infectious and healing complications after elective orthopaedic foot and ankle surgery during tumor necrosis factor-alpha inhibition therapy. *Foot Ankle Int* 2004;**25**:331–5.
7 **Lipsky PE**, Van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, *et al*. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant study group. *N Engl J Med* 2000;**343**:1594–602.
8 **Hanauer SB**, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, *et al*. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;**359**:1541–9.
9 **Kroesen S**, Widmer AF, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. *Rheumatology (Oxford)* 2003;**42**:617–21.
10 **Giles JT**, Gelber AC, Nanda S, Bartlett SJ, Bathon JM. TNF inhibitor therapy increases the risk of post operative orthopaedic infection in patients with rheumatoid arthritis [abstract]. *Arthritis Rheum* 2004;**50**(suppl):S660.

Increase in methotrexate dose in patients with rheumatoid arthritis who have an inadequate response to infliximab

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The strategy needed for patients with inadequate response to treatment with infliximab and methotrexate (MTX) is not well defined. It has been suggested that an increase in the infliximab dosage, a shortening of the intervals between infusions, or a switch to another anti-tumour necrosis factor α agent might provide clinical benefit.[1–4] Another, less expensive, strategy might be to increase the MTX weekly dose in patients not co-treated with MTX at the maximal dose. This study aimed at evaluating the efficacy of increasing the MTX dose in patients with rheumatoid arthritis (RA) with active disease despite treatment with infliximab and MTX.

METHODS AND RESULTS

Data were obtained from six rheumatology departments that measure the 28 joint count Disease Activity Score (DAS28) before each infliximab infusion. All patients with RA with active disease (DAS28 ⩾3.2), despite treatment with a stable regimen of infliximab (3 mg/kg at 0, 2, 6 weeks, thereafter every 8 weeks) and MTX, in whom the MTX weekly dose was increased in order to obtain a better disease control, were included. The exclusion criteria were a change in corticosteroid daily dose or in infliximab regimen at the time of the change of MTX dose, or during the 16 weeks following. The DAS28 scores obtained at the first and second infusion after the change in MTX dose were compared with those obtained before the change (Wilcoxon paired test), and the percentages of responders (EULAR criteria) at the first and second infliximab infusion after the adjustment in MTX dosage were obtained.

A total of 22 patients with RA were included (15 female and 7 male, mean (SD) age 47 (9.1) years, mean (SD) disease duration 7.3 (3.9) years). At the time of adjustment of MTX dosage, patients had been treated with MTX and infliximab for a mean (SD) of 7.6 (6.4) months. The mean (SD) MTX weekly dose was increased from 9.9 (3.9) mg to a mean of 15 (4.3) mg because of primary (n = 8), or secondary infliximab treatment failure (n = 7) or because the response was judged to be insufficient (n = 7). The change was tolerated well in all patients. The DAS28 scores decreased significantly after the MTX dose adjustment (table 1). Five (23%) patients were considered as responders at 8 weeks (four moderate and one good response) and eight (36%) at 16 weeks (seven moderate and one good response) (fig 1). However, according to the EULAR criteria, 21 (95%) of the patients presented with active disease (DAS28 ⩾3.2) 16 weeks after the adjustment, and a disease remission (DAS28 ⩽2.6) was never observed.

DISCUSSION

These results might be regarded as disappointing: the mean disease activity showed only modest improvements, and the disease remained active in most patients. However, a response was observed in more than a third of the patients, a percentage which cannot be considered as anecdotal. This study was an observational cohort study, so it cannot be claimed that an increase in MTX dose is useful in patients with active disease despite infliximab treatment, because two main hypotheses can be put forward for explanation: (*a*) the increase in the MTX dose induces a clinical response in a relevant number of patients; (*b*) the observed results are due to a regression to the mean effect; adjustment in the MTX dose is likely to be proposed when disease activity increases, so the observed improvement in disease activity might have occurred without a change in the MTX dose. Such a hypothesis was recently proposed to explain the improvement observed after infliximab dose escalation.[5]

Table 1 Disease activity before, and at the first (8 weeks) and second (16 weeks) infliximab infusion after MTX dose adjustment

		After adjustment	
	Before adjustment	First infliximab infusion	Second infliximab infusion
MTX dose (mg/weekly)	9.9 (3.9)	15 (4.3)	15 (4.3)
DAS28	5.2 (0.8)	4.7 (1.1)*	4.5 (0.9)**
Tender joint count (/28)	10.2 (7)	7.7 (7)*	7.4 (7)*
Swollen joint count (/28)	5.2 (4)	4.8 (4)	3.7 (4)
ESR (mm/ 1st h)	32.1 (21)	28.9 (17)	27.2 (17)
Patient global assessment (/100)	52.2 (17)	44 (23)	42 (18)*

Results are shown as mean (SD).
*p<0.05; **p<0.01.

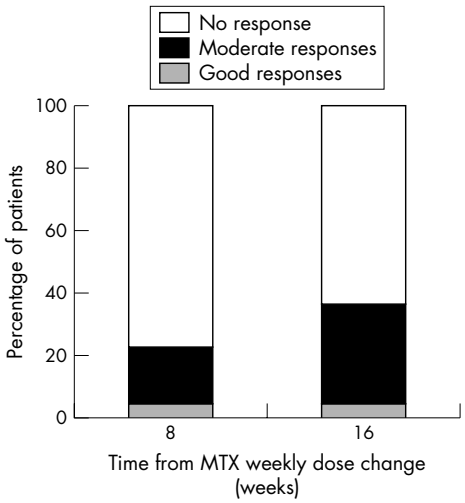

Figure 1 percentage of patients with good and moderate response (EULAR criteria) 8 and 16 weeks after an increase in the MTX weekly dose.

Further prospective studies are needed to determine the precise strategy to be used in patients with active RA despite infliximab treatment. While waiting for these, an increase in the MTX dose might be an inexpensive but well tolerated strategy which might be used as a first therapeutic option, or in combination with other changes in treatment for patients not treated with MTX at a maximal dose.

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REFERENCES

1 **Sidiropoulos P**, Bertsias G, Kritikos HD, Kouroumali H, Voudouris K, Boumpas DT. Infliximab treatment for rheumatoid arthritis, with dose titration based on the Disease Activity Score: dose adjustments are common but not always sufficient to assure sustained benefit. *Ann Rheum Dis* 2004;**63**:144–8.
2 **Haraoui B**. Is there a rationale for switching from one anti-tumor necrosis factor agent to another? *J Rheumatol* 2004;**31**:1021–2.
3 **Favalli EG**, Arreghini M, Arnoldi C, Panni B, Marchesoni A, Tosi S, *et al*. Anti-tumor necrosis factor alpha switching in rheumatoid arthritis and juvenile chronic arthritis. *Arthritis Rheum* 2004;**51**:301–2.
4 **Stern R**, Wolfe F. Infliximab dose and clinical status: results of 2 studies in 1642 patients with rheumatoid arthritis. *J Rheumatol* 2004;**31**:1538–45.
5 **Van Vollenhoven RF**, Brannemark S, Klareskog L. Dose escalation of infliximab in clinical practice: improvements seen may be explained by a regression-like effect. *Ann Rheum Dis* 2004;**63**:426–30.

The T348M mutated form of cryopyrin is associated with defective lipopolysaccharide-induced interleukin 10 production in CINCA syndrome

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The term autoinflammatory disease has been proposed to describe a group of disorders characterised by attacks of seemingly unprovoked inflammation without increased levels of autoantibodies or increased numbers of autoreactive T cells. Such inflammatory conditions are often associated with mutations of genes of the pyrin superfamily. For instance, mutations in cryopyrin (CIAS1, NALP3, PYPAF1) have been found in about 50% of patients with CINCA syndrome.[1] These patients are characterised by neonatal onset of cutaneous symptoms, chronic meningitis, and joint manifestations with recurrent fever and inflammation. Despite the description of several mutations within the cryopyrin gene,[1 2] it remains unclear how the resulting amino acid changes modify the function of this protein and why inflammation develops under these conditions. A recent study demonstrated increased spontaneous interleukin (IL) 1 production by macrophages expressing the R260W mutated form of cryopyrin.[3]

METHODS AND RESULTS

We identified a patient with CINCA syndrome who had a T348M mutation of the cryopyrin gene using genomic DNA extracted from whole blood, as described previously.[1] Because cryopyrin is largely expressed in monocytes and neutrophils, we performed functional in vitro tests using blood leucocytes of this patient (table 1) at three time points: A. medium inflammatory activity (9.59×10^9 blood neutrophils/l); B. high inflammatory activity (14.950×10^9/l); and C. low

Table 1 Patient characteristics

41 year old man
Periodic fever and a generalised maculopapular itching erythematous rash since the age of about 8 months
Arthralgia and arthritis with transient swelling beginning in the first year of life
Perceptive deafness beginning after about 30 years
Suffering from abdominal pain and persistent haemorrhagic diarrhoea with increasing age
No increased levels of autoimmune antibodies
Skin histology: cellular infiltrate mainly containing neutrophils
Cranial MRI: internal hydrocephalus and empty sella
Lumbar puncture: sterile chronic meningitis
No growth or mental retardation